Two Generalizations of the Design of Experiments Methodology for Enhanced Process Understanding

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Machine Learning Algorithms for Chemical Reaction Systems

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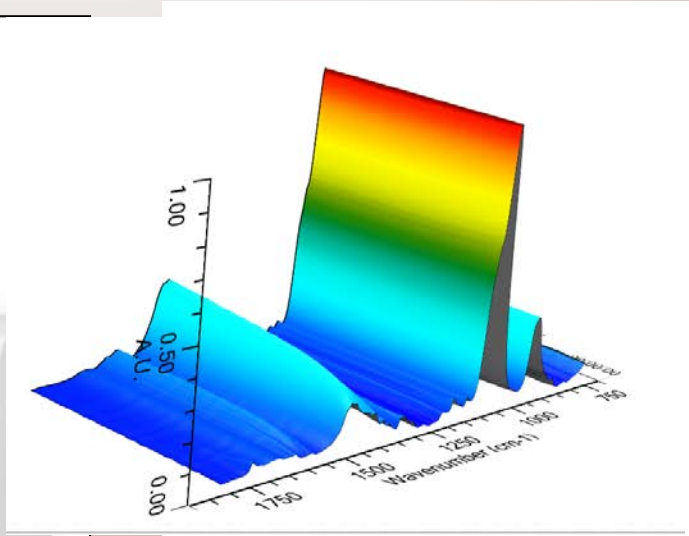
Types of Models

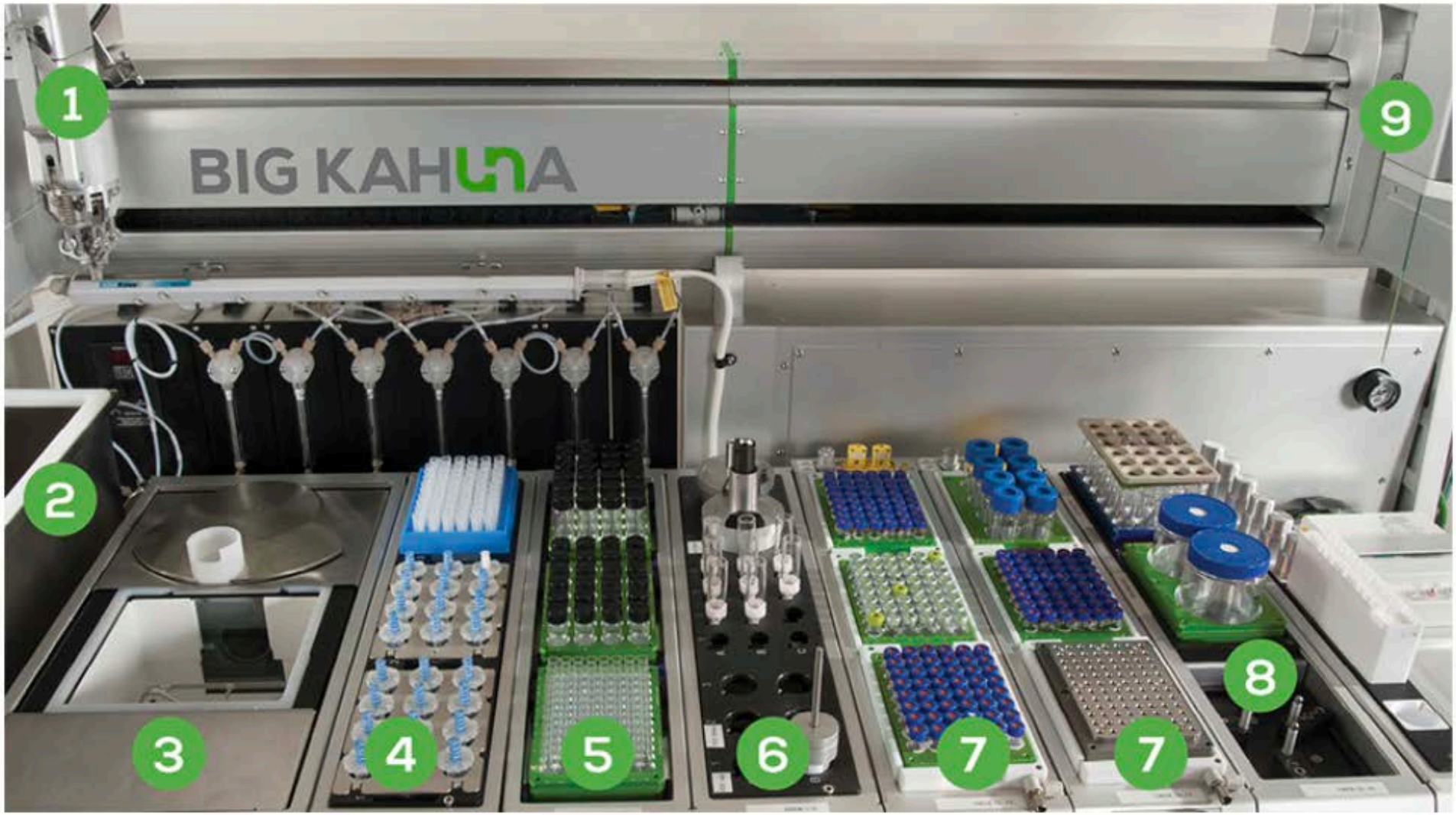
- Knowledge-Driven Models
  - Instead of "Fundamental" or "First Principles"
- Data-Driven Models
  - No knowledge of Inner Workings of Process
- Hybrid Models
  - Partial Knowledge + Data
- ***Models Should Have a Purpose***
  - Change the Purpose → Change the Model
    - Models for Kinetics, Process Design, Optimization, Control …
    - Conceptual, Physical (Pilot Plant), Mathematical, …

Plethora of Robotic Devices



If You have One … Million $

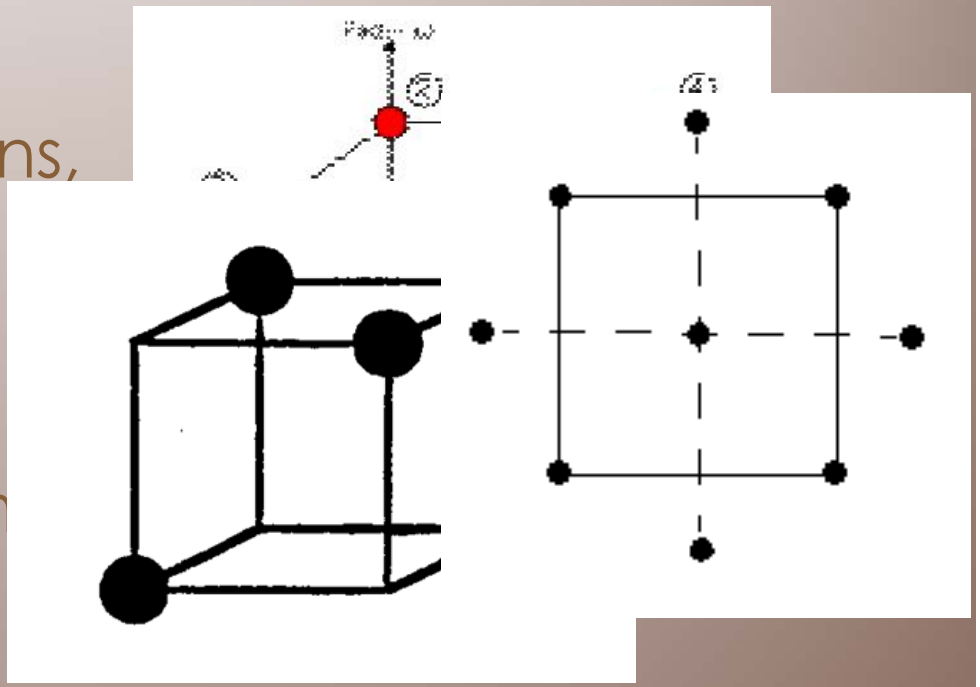
The Age of Big Data



Design Experiments - Analyze Data

Design of Experiments (DoE)

- Very Powerful Methodology 50 Years Young!
- ***Never Change One Condition at a time***
- Full Factorial Designs,
- Fractional Factorial Designs,
  - ½ fraction: 2^{n-1}
  - ¼ fraction: 2^{n-2}
  - 1/8 fraction: 2^{n-3}
- Center Composite Design
  - …



Is DoE Sufficient?

My Answer is: **NO**

1st Generalization: DoE ➔ DoDE

- Time-Varying Inputs (Factors)
  - Design of Dynamic Experiments (DoDE)
    - Batch Reactor Temperate vs. Time, T(t)=?
    - Feeding of Bioreactor with Sugar Source, u(t)=?
    - Bioreactor pH vs. Time, pH(t)=?
  - How Many Dynamic Experiments?
  - How we Design them?

Georgakis, C., (2013) *"Design of Dynamic Experiments: A Data-Driven Methodology for the Optimization of Time-Varying Processes"* Ind. Eng. Chem. Res. **52** (35):12369-12382

2nd Generalization: RSM ➔ DRSM

- RSM: Response Surface Methodology
  - Interpolative Polynomial Model of Output
  - $y = \beta_0 + \sum_{i=1}^{n} \beta_i X_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta_{ij} X_i X_j + \sum_{i=1}^{n} \beta_{ii} X_i^2$
- Composition Measurements every Hour
  - For 12 hrs ➔ 12 RSMs ??
- **DRSM:** Dynamic Response Surface Method

$$y(t) = \beta_0(t) + \sum_{i=1}^{n} \beta_i(t) X_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta_{ij}(t) X_i X_j + \sum_{i=1}^{n} \beta_{ii}(t) X_i^2$$

- $\beta_q(t) = \gamma_{q,1} P_0(t) + \gamma_{q,2} P_1(t) + \cdots \gamma_{q,R} P_{R-1}(t)$
  - $P_i(t)$ the i[th] Shifted Legendre Polynomial
  - $P_0 = 1,\ P_1(t) = -1 + 2t,\ P_2(t) = 1 - 6t + 6t^2$

DoDE: Time-Varying Inputs

- Define Time-Varying Input Domain
- Define Time-Varying Coded Variable, z(τ)

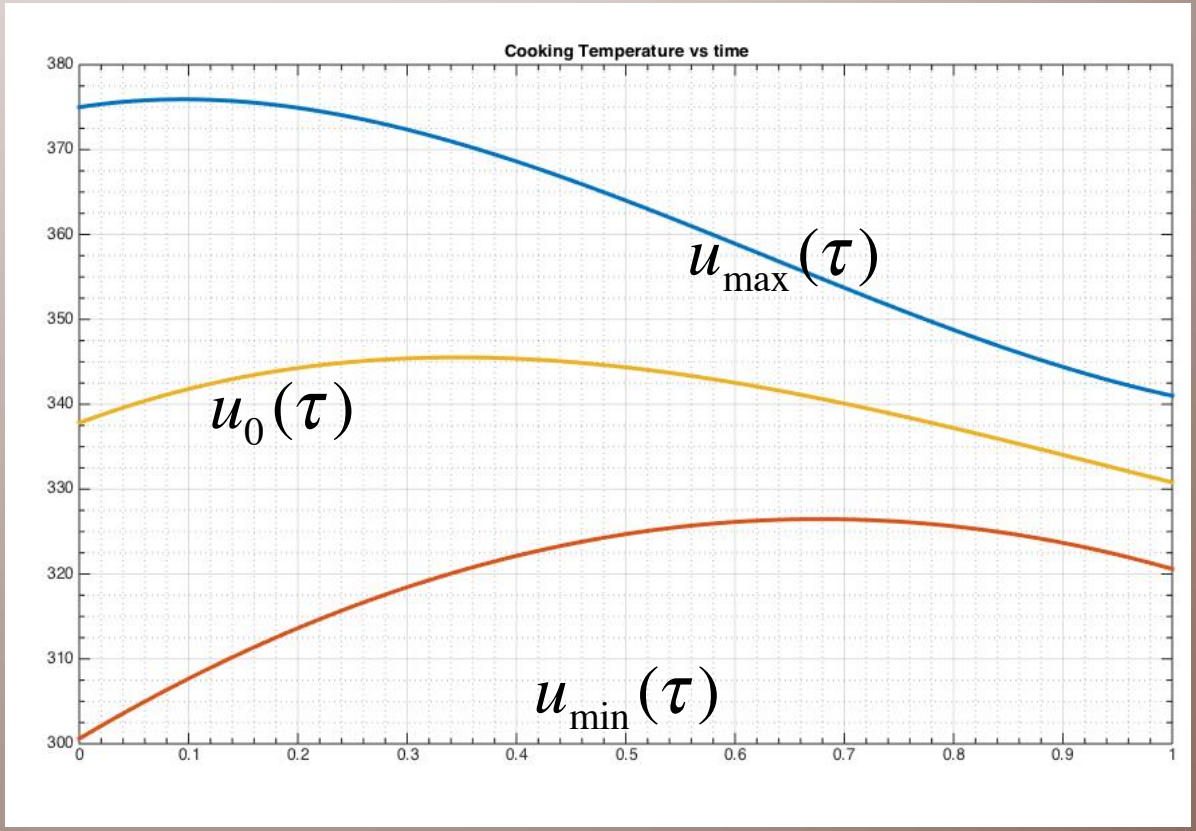
$$u_0(\tau) = \frac{u_{\max}(\tau) + u_{\min}(\tau)}{2}$$

$$\Delta u(\tau) = \frac{u_{\max}(\tau) - u_{\min}(\tau)}{2}$$

$$z(\tau) = \frac{u(\tau) - u_0(\tau)}{\Delta u(\tau)}$$

$$-1 \le z(\tau) \le +1, \quad \tau = t / t_b$$

$$u(\tau) \triangleq u_0(\tau) + \Delta u(\tau) z(\tau)$$

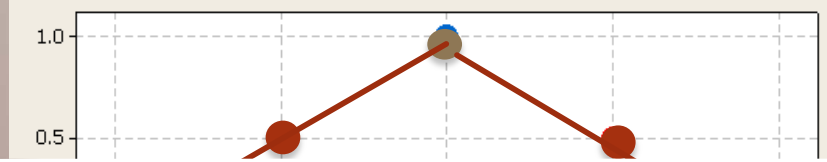


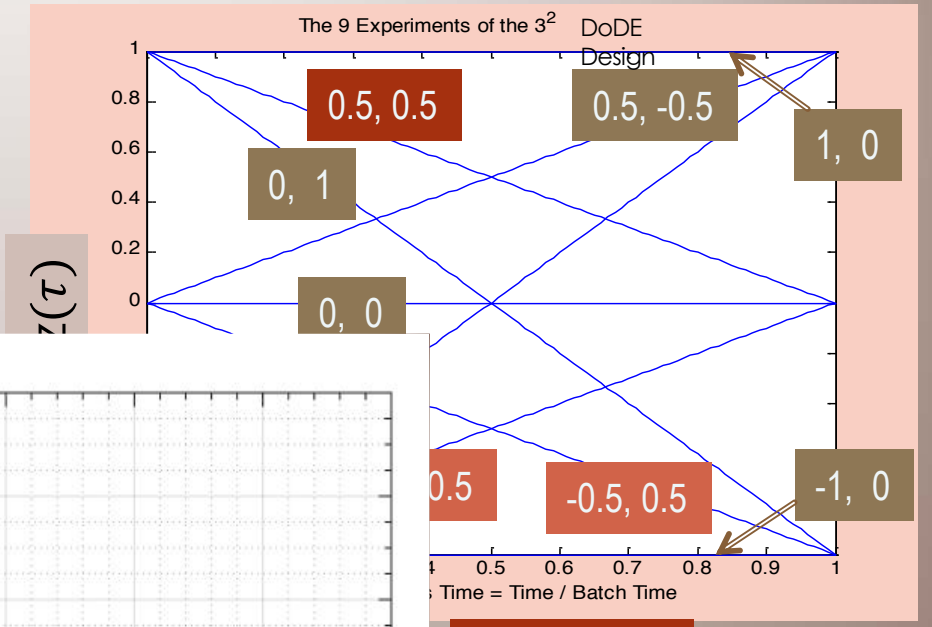
Main Idea: $z(\tau) = a_1 P_0(\tau) + a_2 P_1(\tau) + a_3 P_2(\tau) + \cdots$

Nine (9) Time-Varying Inputs

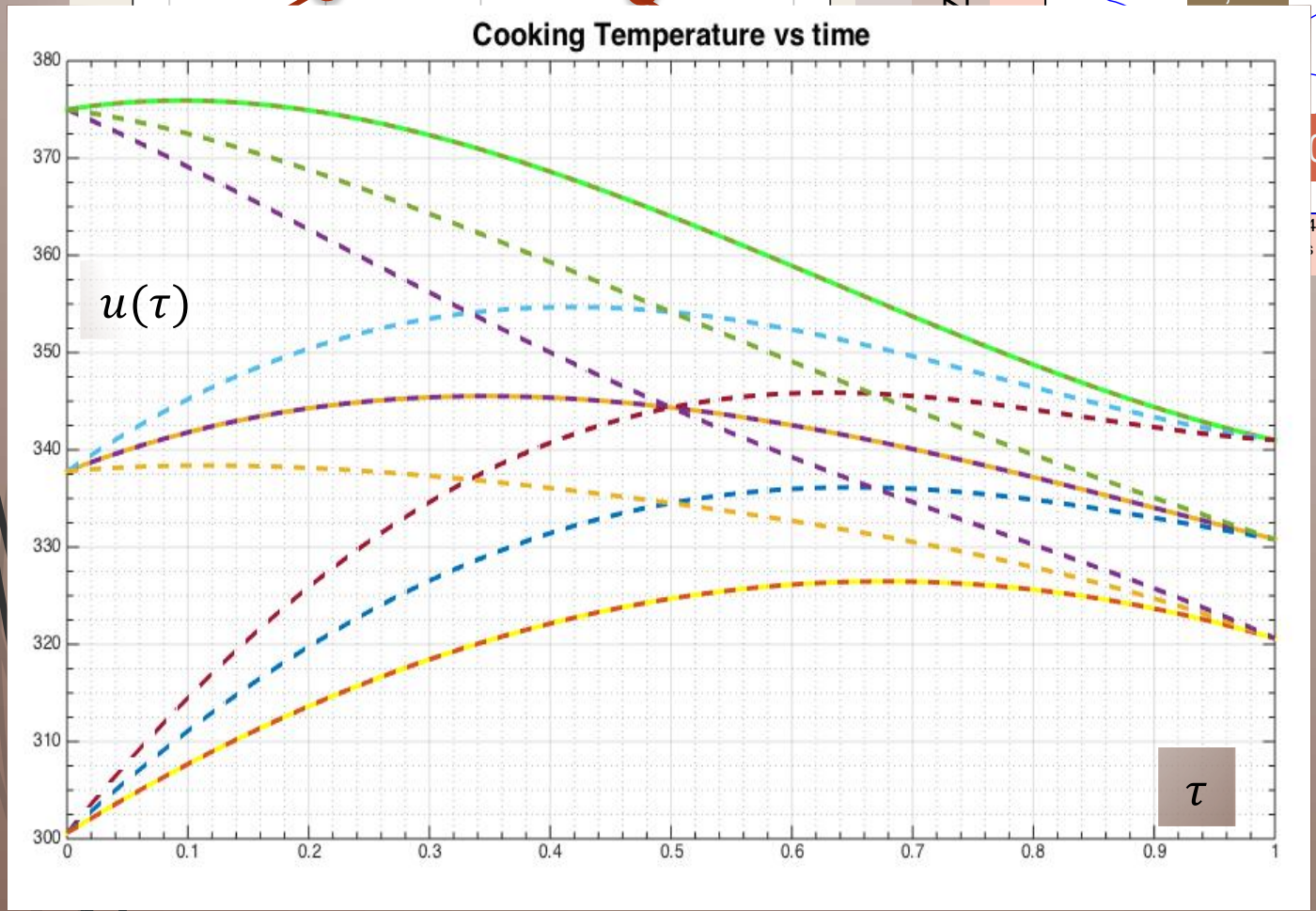
$$z(\tau) = a_1 P_0(\tau) + a_2 P_1(\tau)$$

$$-1 \le a_1 \pm a_2 \le +1 \Leftrightarrow -1 \le z(\tau) \le +1$$





$$\tau = t/t_b$$



DoDE Example: Batch Reactor

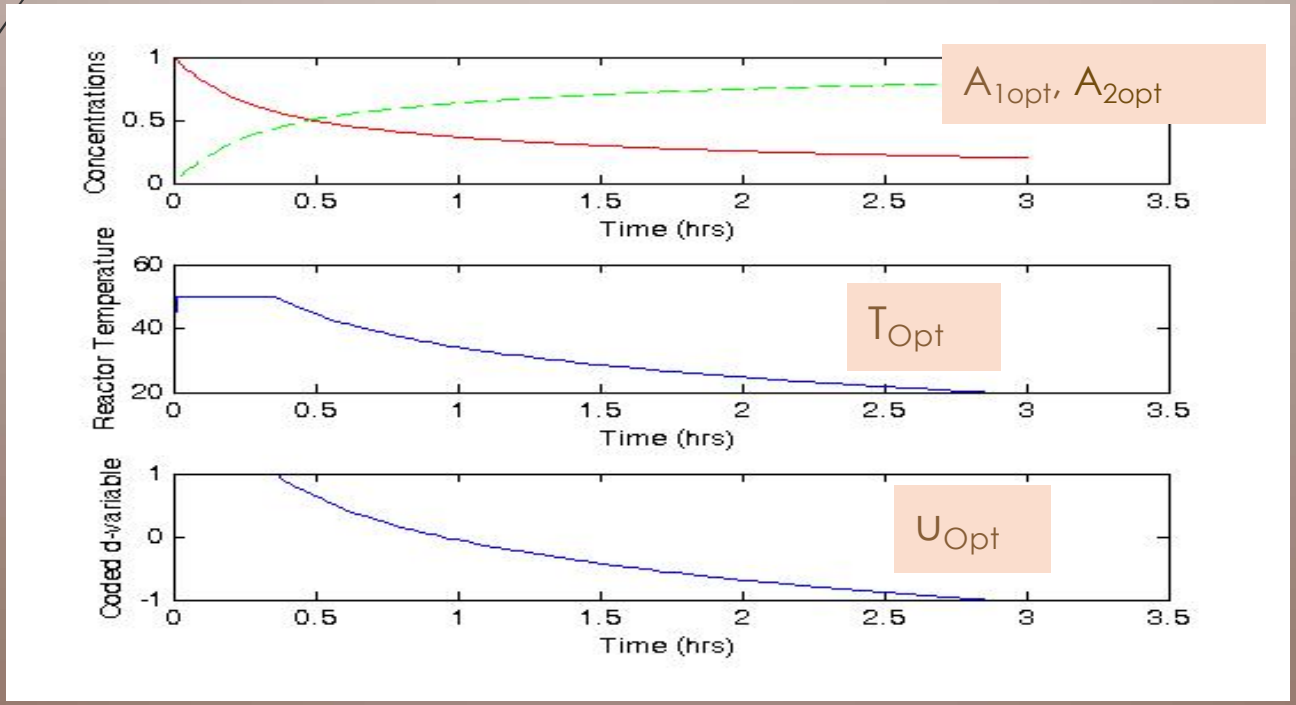
Reversible Reaction in Batch

$A_1 \rightleftharpoons A_2$ (15 < T < 50 °C)

$$\boldsymbol{r = k_1 A_1 - k_2 A_2} \qquad k_i = k_{i0} \exp\left(-\frac{E_i}{RT}\right) \; with \quad E_2 > E_1$$

Model-based Optimum Conversion: **74.6%**

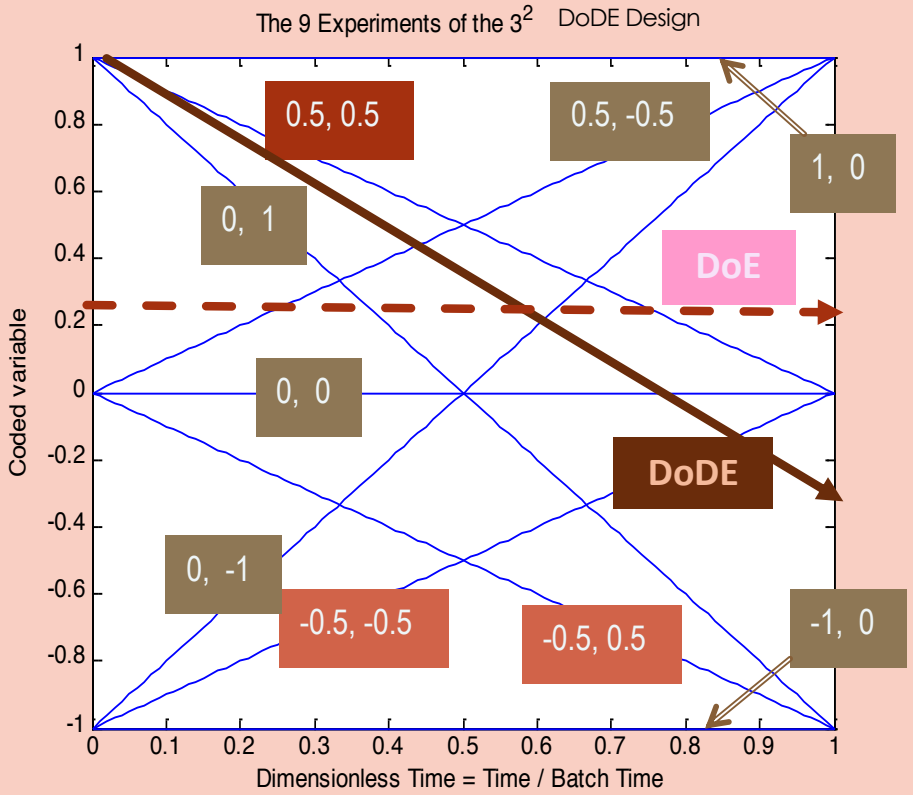
Decreasing Temperature Profile



Optimization via DoDE

- Two Factors: T Level & Linear Slope
  - Nine DoDE Experiments
    - Linear in Time
    - between 15^{0}C to 50^{0}C
  - Optimization:
    - Max DoDE Conversion
      - x=74.3%,
      - T* 50^{0}C → 28^{0}C

74.6%



	DoE	DoDE	MBO
Conversion	71.4%	74.3%	74.6%
Difference from MBO	3.2	0.3	

VERY Small Difference

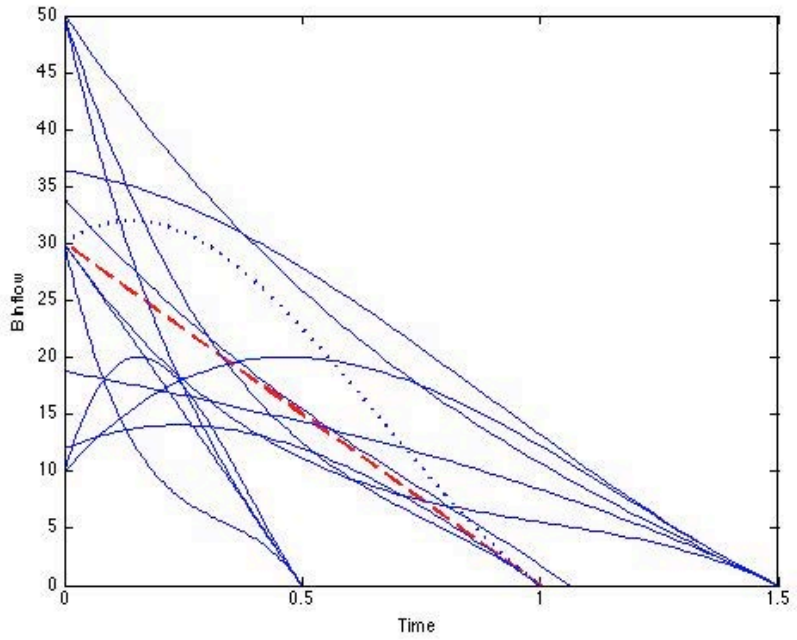
DoDE Semi-Batch Reactor

Tufts UNIVERSITY

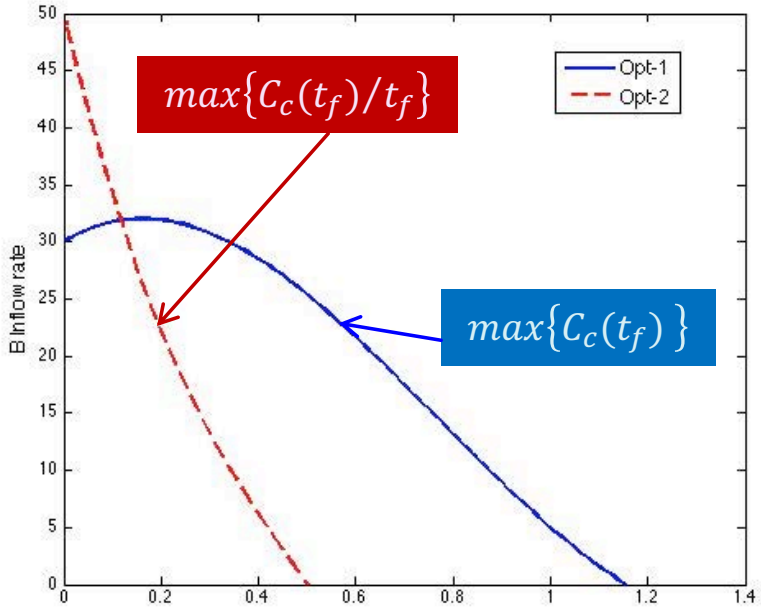
Reaction Example:

$$Rxn1:\ A + B \longrightarrow C \quad r_1 = k_1 C_A C_B, k_1 = 2\ l\ mol^{-1} h^{-1}$$
$$Rxn2:\ 2B \longrightarrow D, \quad r_2 = k_2 C_B^2,\ k_2 = 1\ l\ mol^{-1} h^{-1}$$
$$Rxn3:\ C \longrightarrow E, \quad r_1 = k_3 C_C,\ k_3 = 1\ h^{-1}$$

DoDE Runs: Feeding B

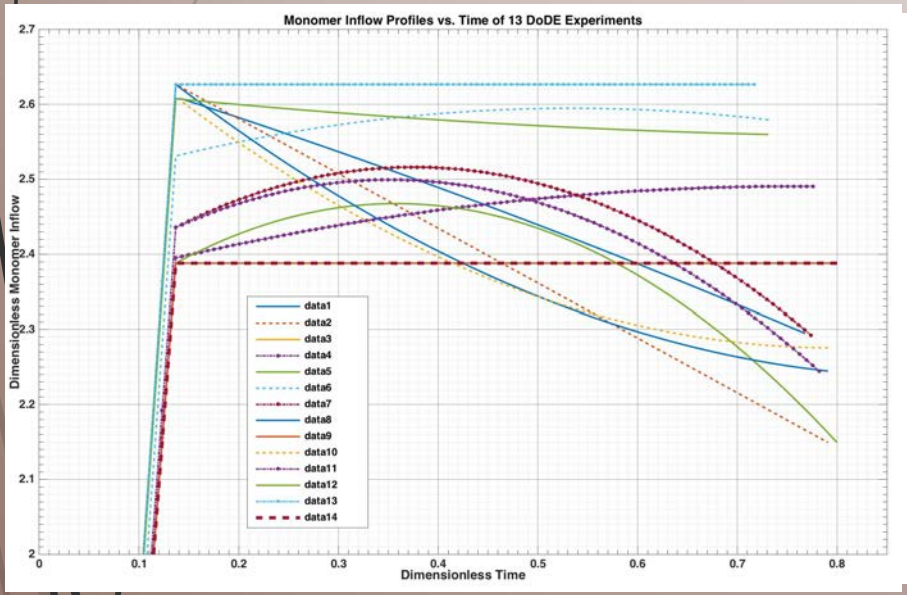


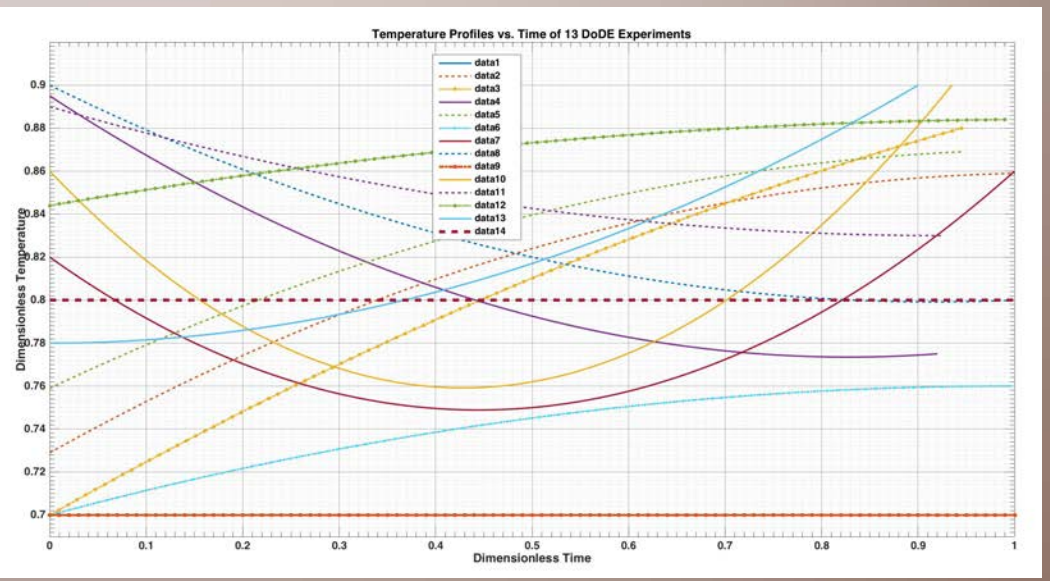
Optimal Runs



DoDE: The Dow Project

- Polymerization ➔ Increase Productivity
  - **NO** Detailed Knowledge-Driven Process Model
- Inputs (factors) Can Vary with Time





15 DoDE experiments ➔ Batch Time Reduced by 20%
Productivity Increase by 20%

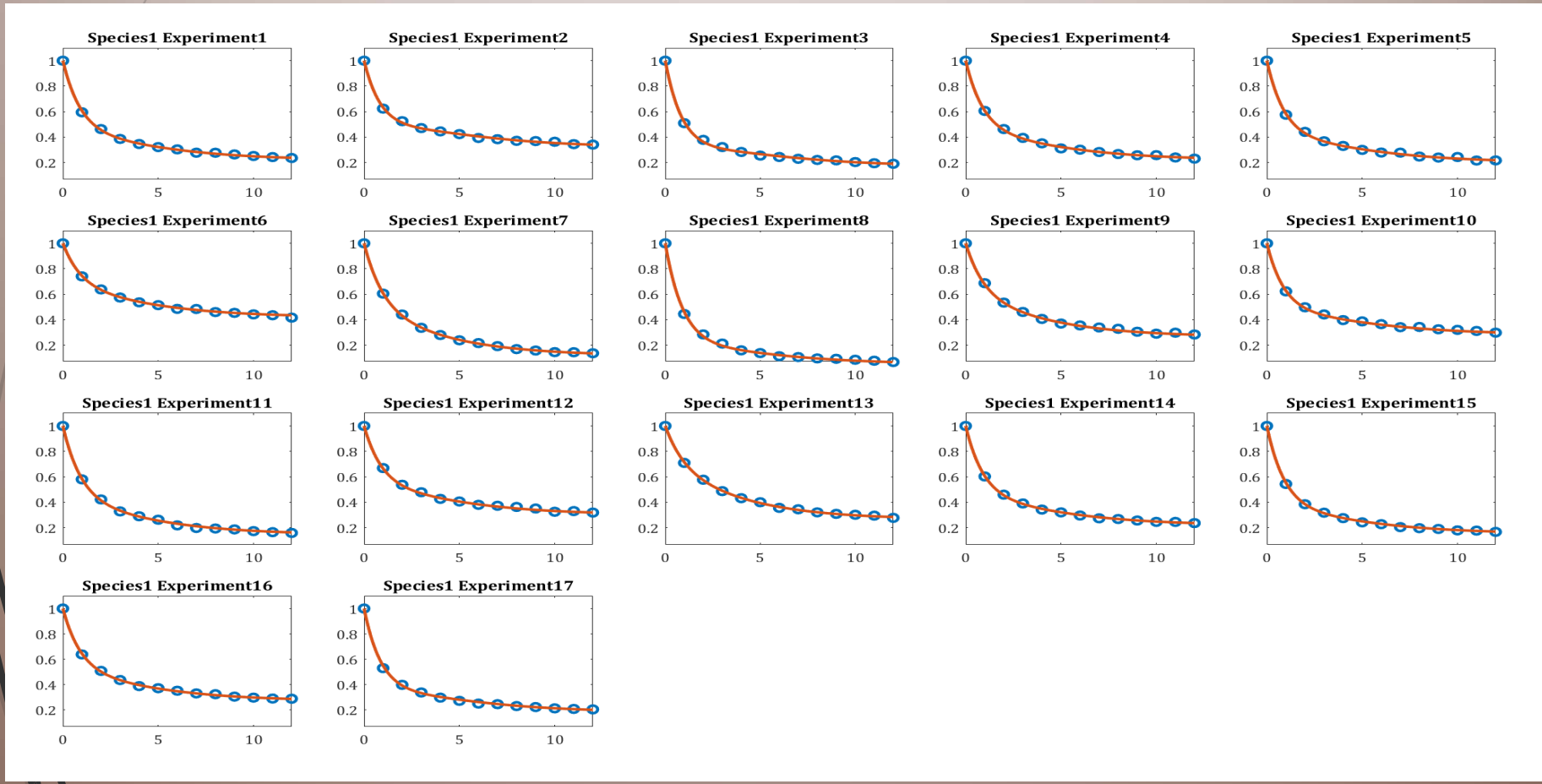
The DRSM Idea

- From RSM:
  - $y = \beta_0 + \sum_{i=1}^{n} \beta_i X_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta_{ij} X_i X_j + \sum_{i=1}^{n} \beta_{ii} X_i^2$
- To DRSM:
  - $y(t) = \beta_0(t) + \sum_{i=1}^{n} \beta_i(t) X_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta_{ij}(t) X_i X_j + \sum_{i=1}^{n} \beta_{ii}(t) X_i^2$
- Parameterization:
  - $\beta_q(t) = \gamma_{q,1} P_0(t) + \gamma_{q,2} P_1(t) + \cdots \gamma_{q,R} P_{R-1}(t)$
    - $q = i, ij, or\ ii$ with $i, j = 1, 2, \ldots, n; j < i$
  - R(parameters) < K(Data per Experiment)
- **DRSM-1: Parametrization with t** ➡ Has Oscillations
- **DRSM-2: Parametrization with** $\theta = \left\{1 - \exp(-\frac{t}{t_0})\right\}$
  - $0 \leq t < \infty \iff 0 \leq \theta < 1$

NO Oscillations - Excellent Model

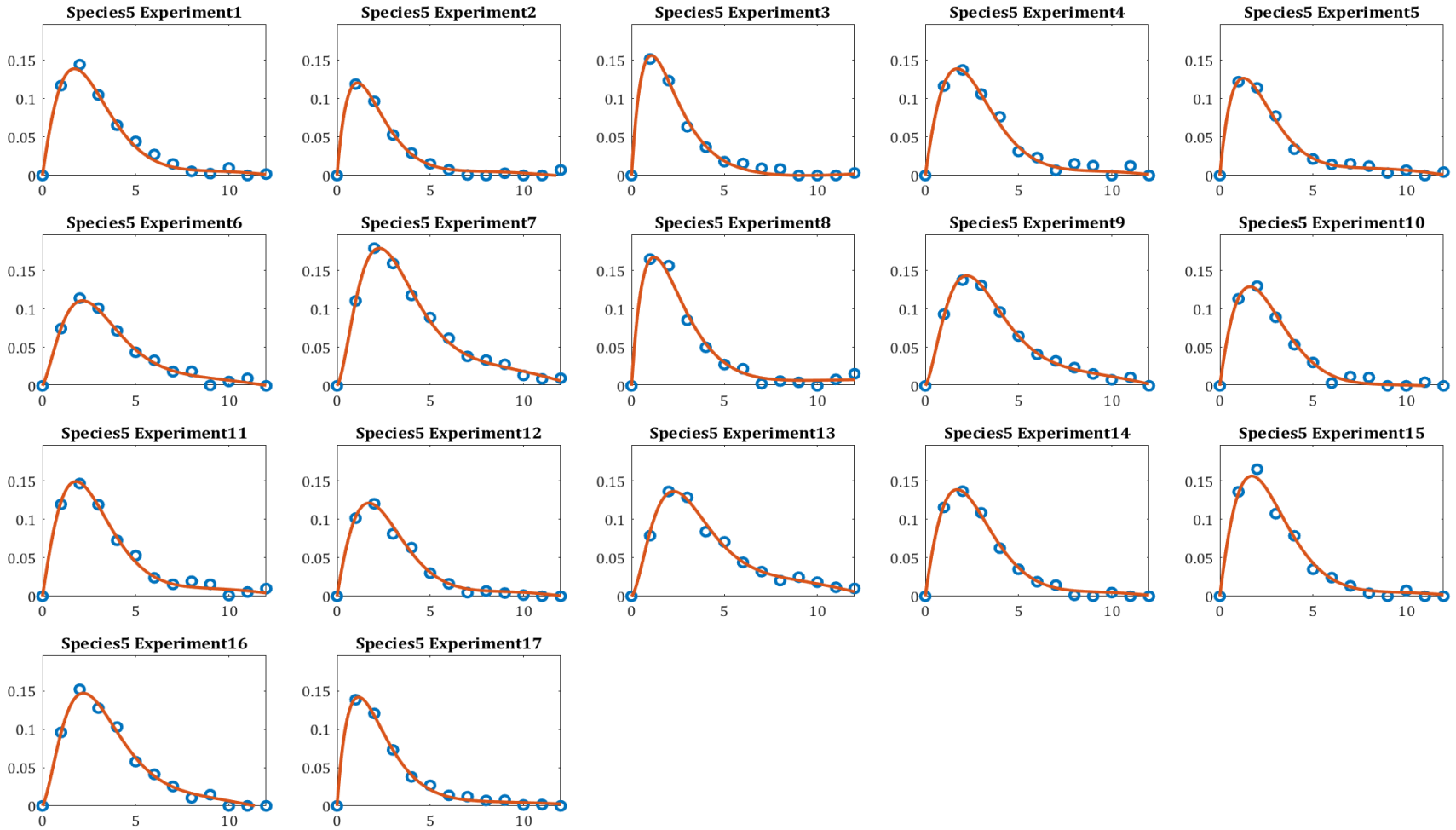
DRSM-2c for **ALL** Pfizer Data: $C_1(t)$

- Time-Resolved **Species 1** Measurements with
- $y(t) = \beta_0(t) + \sum_{i=1}^{n} \beta_i(t) X_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta_{ij}(t) X_i X_j + \sum_{i=1}^{n} \beta_{ii}(t) X_i^2$
  - $R = 3, t_c = 3.3$ All 17 experiments



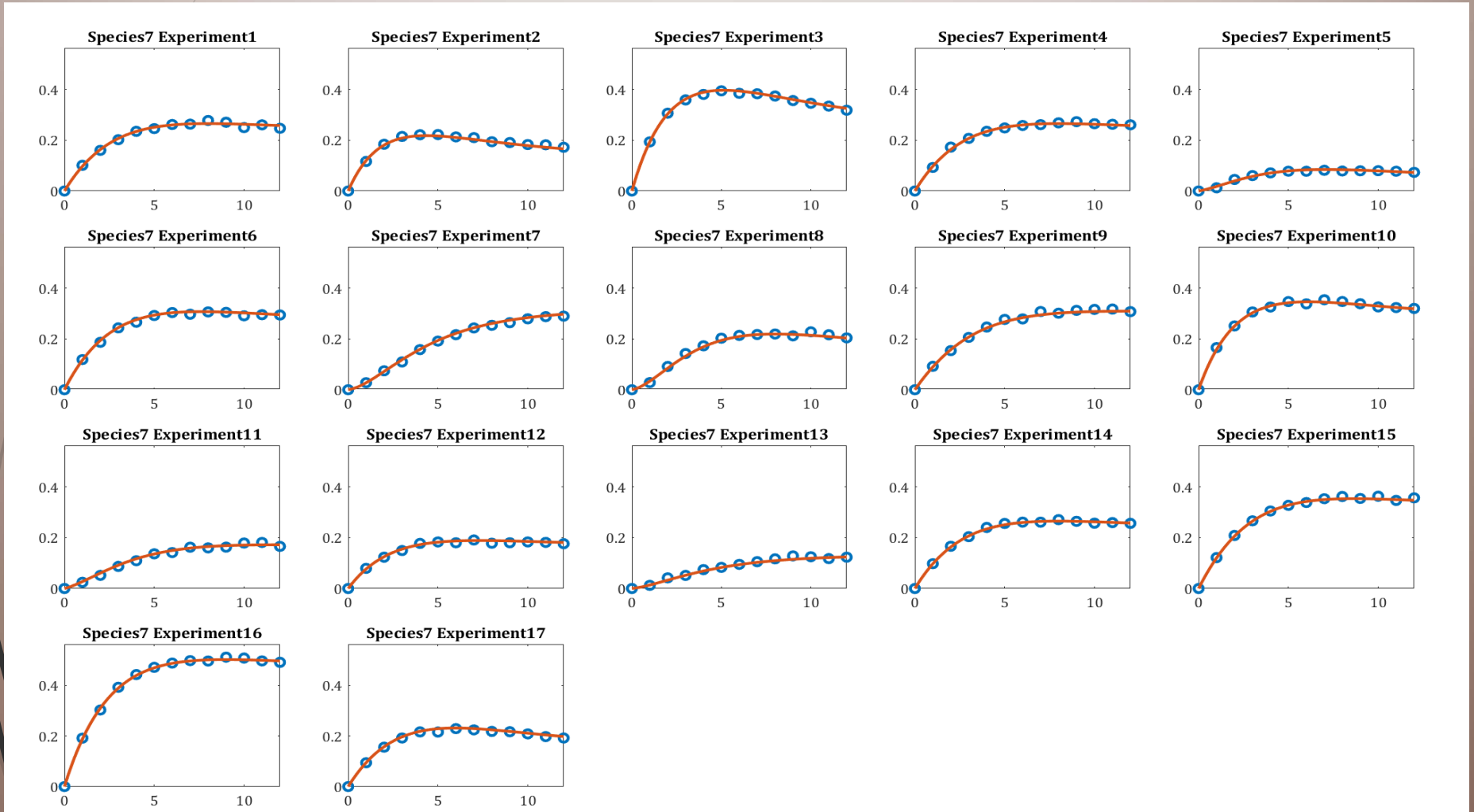
DRSM-2c for **ALL** Pfizer Data: $C_5(t)$

- **Species 5:** $R = 5, t_c = 5.4$



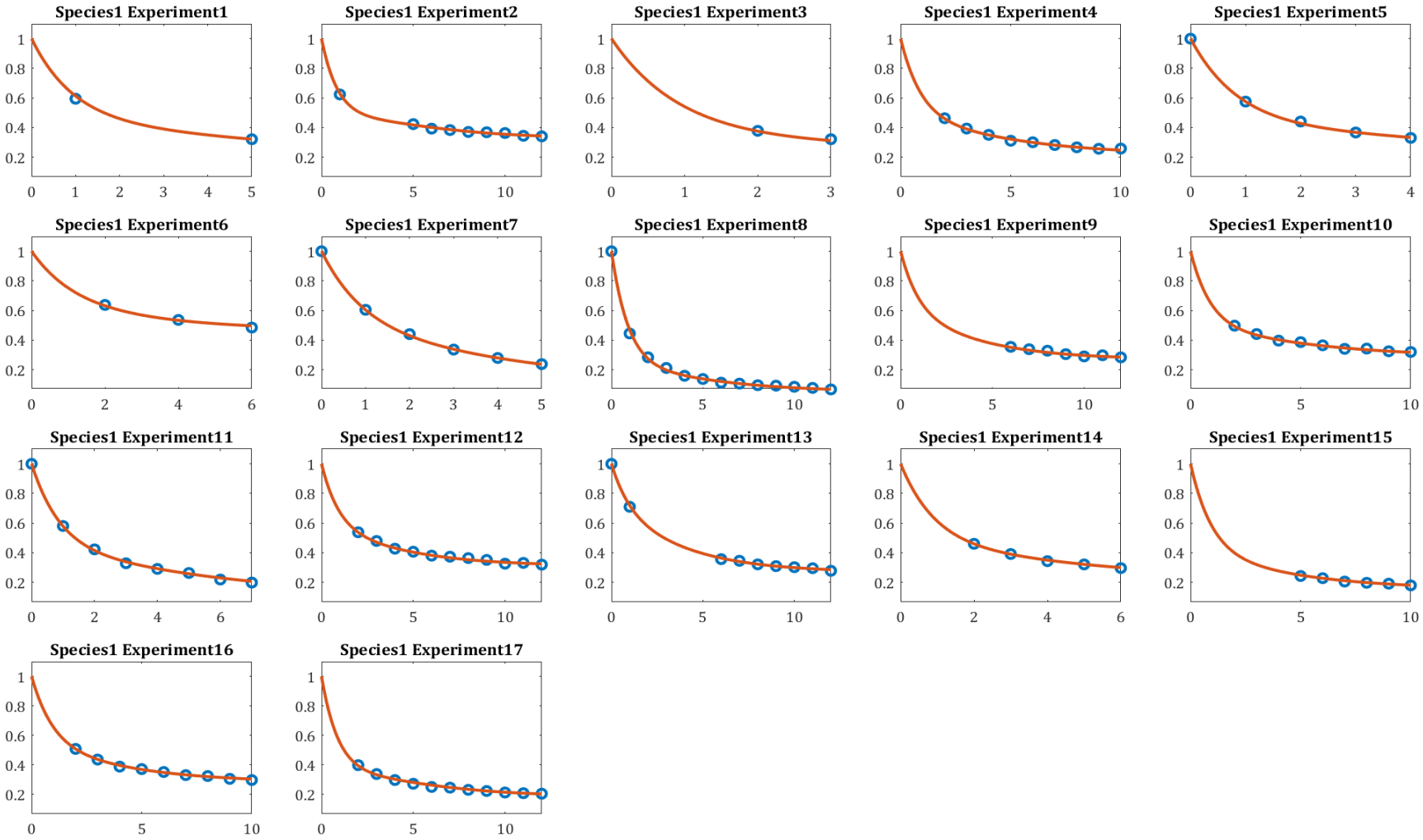
DRSM-2c for **ALL** Pfizer Data: $C_7(t)$

- **Species 7:** $R = 3, t_c = 5.4$



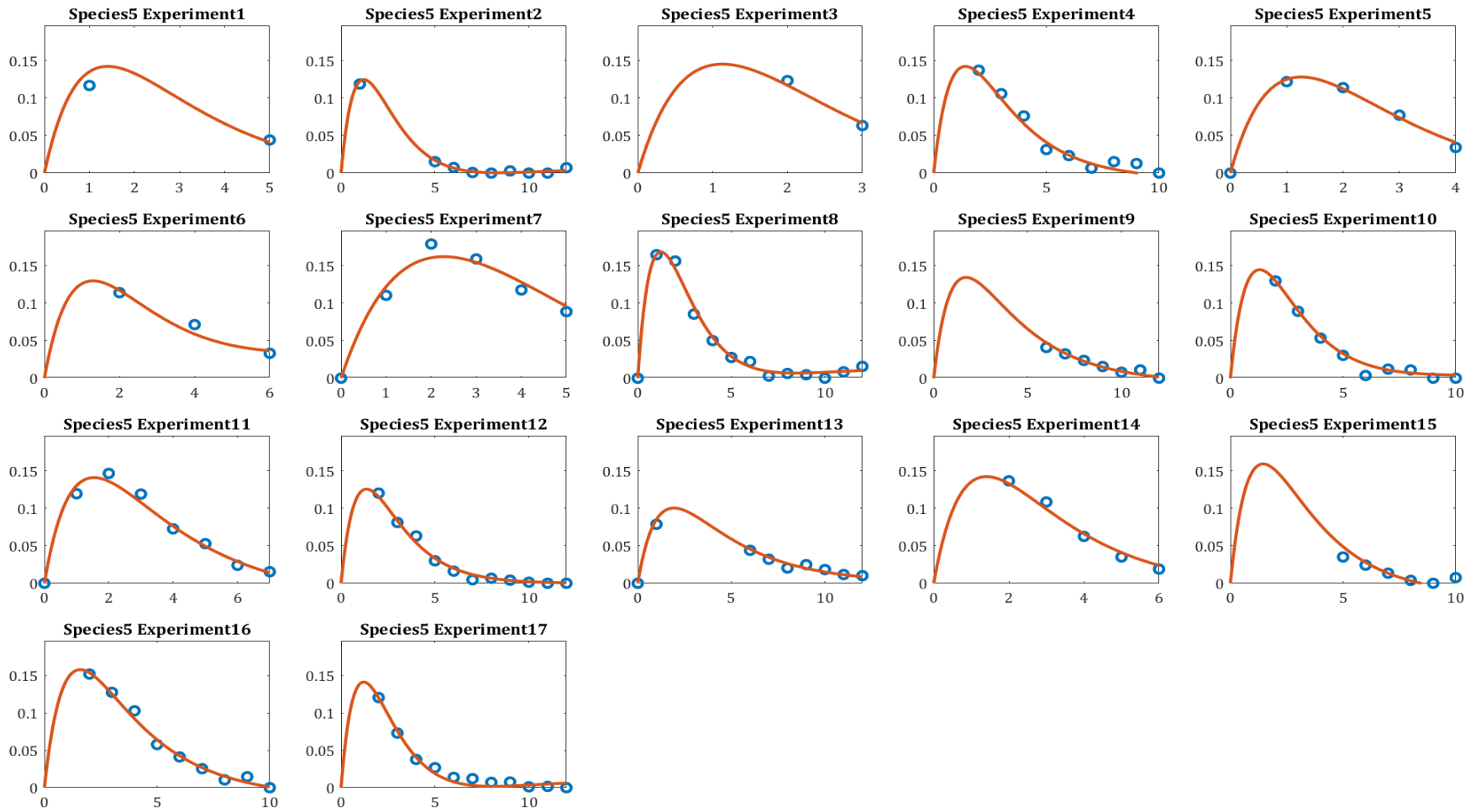
DRSM-2c: **Missing** Pfizer Data: $C_1(t)$

- Species 1: $R = 3, t_c = 3.3$



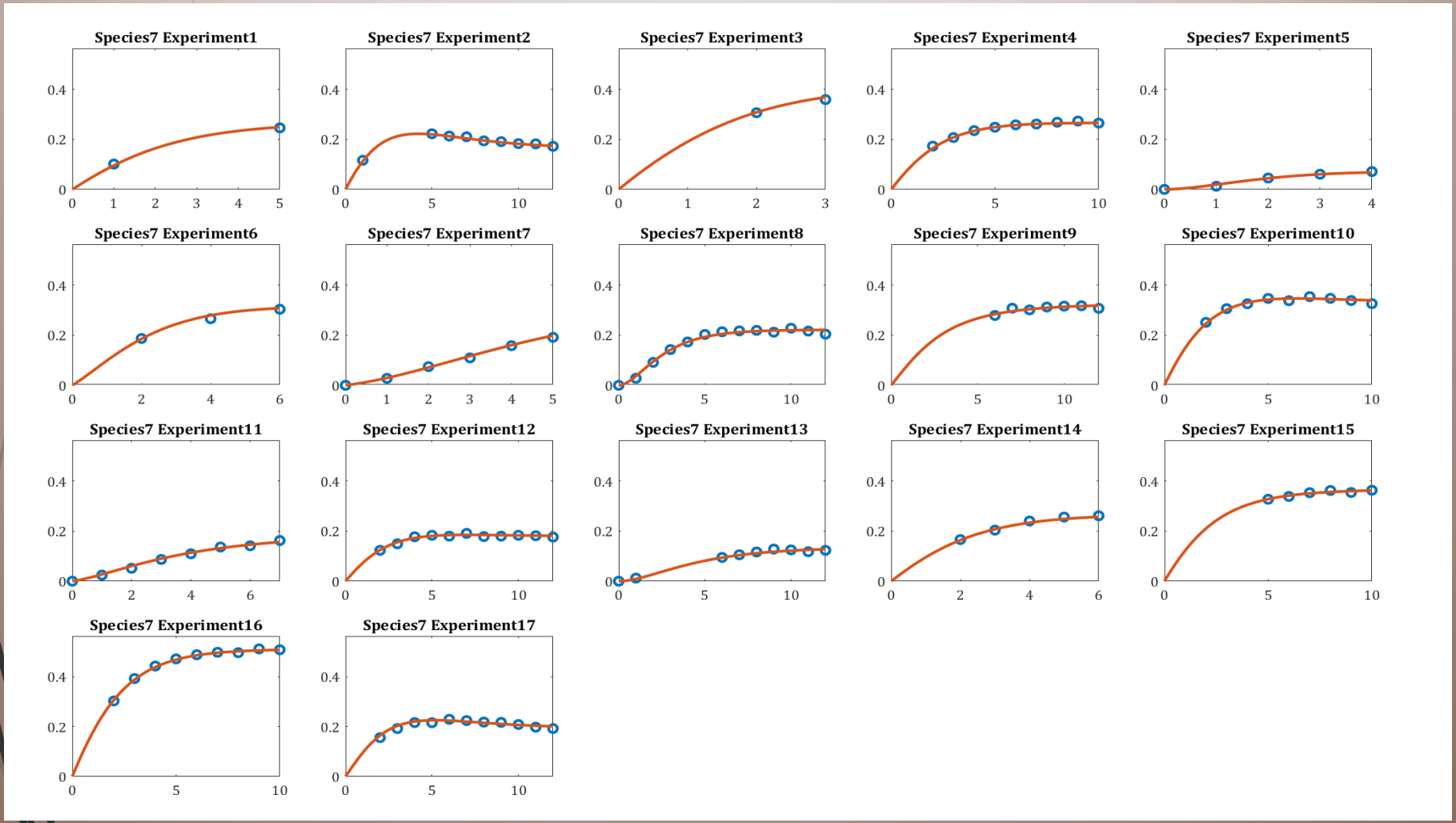
DRSM-2c: **Missing** Pfizer Data: $C_5(t)$

- Species 5: R=3 Tc=3.3

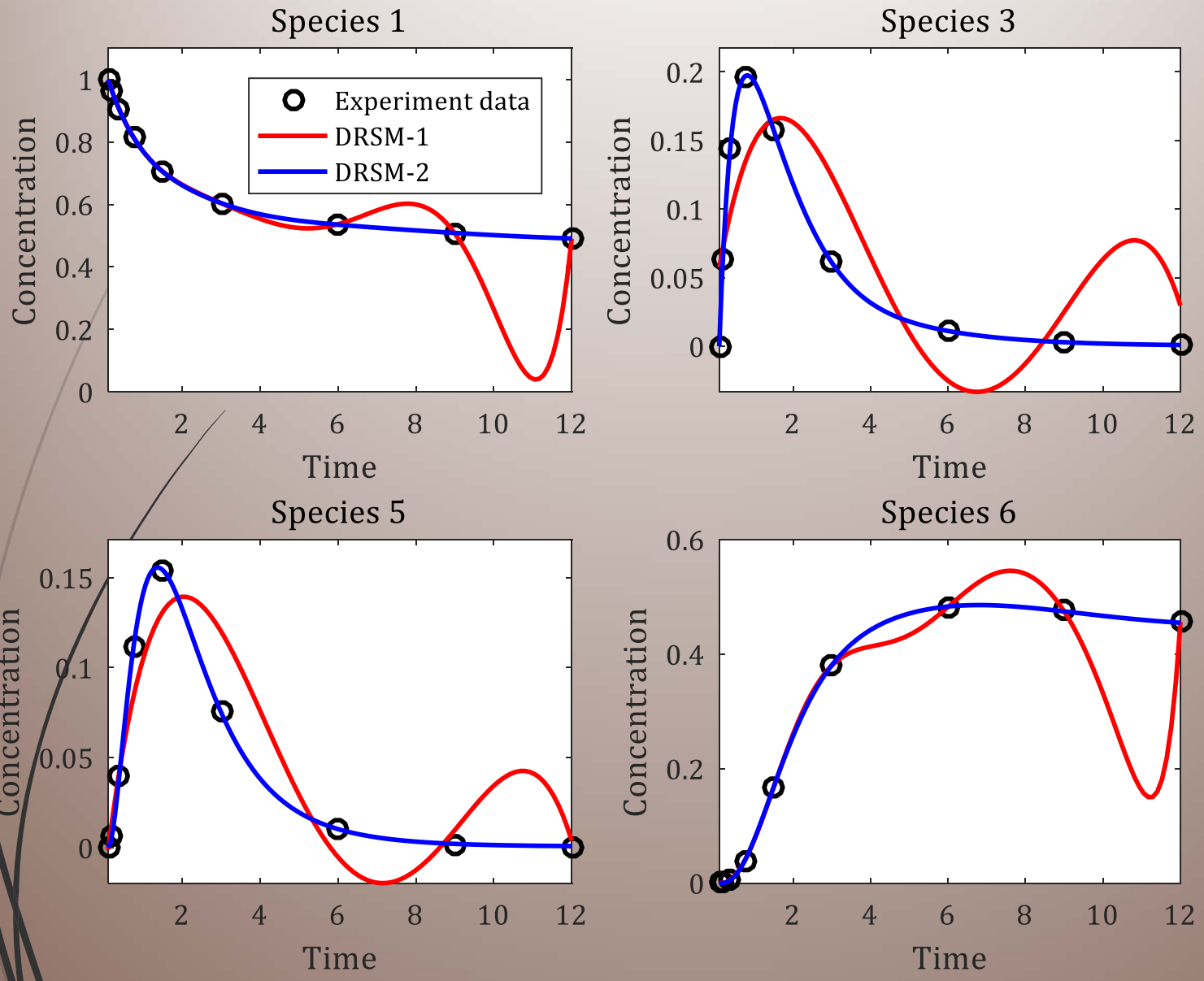


DRSM-2c: **Missing** Pfizer Data: $C_7(t)$

- Species 7: R=3 Tc=3.3

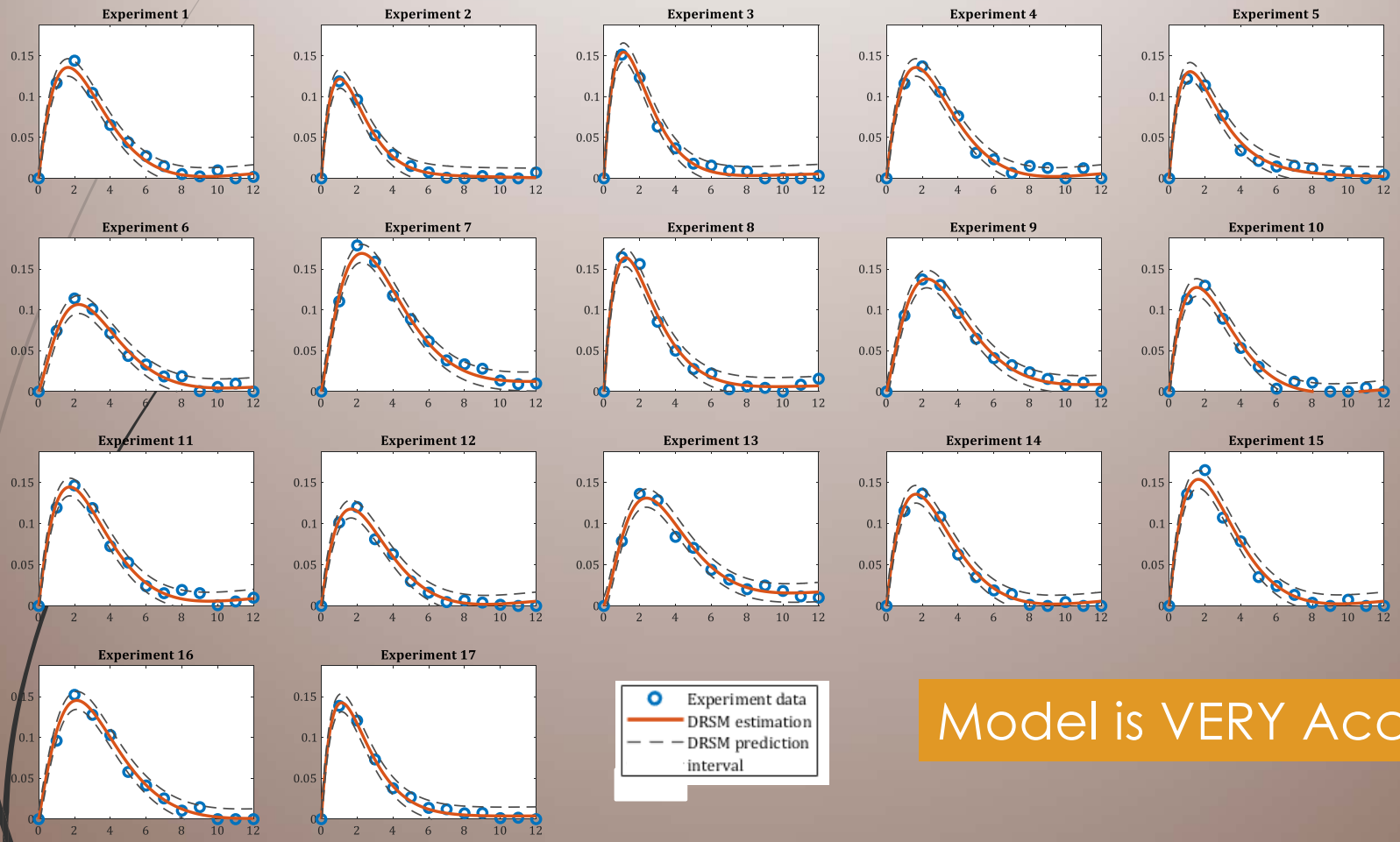


DRSM-2 vs DRSM-1 - Non-equidistant Data



VERY Notable Improvement

Species E with Prediction Interval



Model is VERY Accurate

Fractional Factorial Design (Merck)

- 3 Species and 5 Factors: A, B, C, D, and E
- 2 Blocks: Robotic & Manual
- 6 Data/Batch at ***Unequal*** Intervals

  0, 20, 40, 60, 120, 240 mins
- LC area converted to concentration

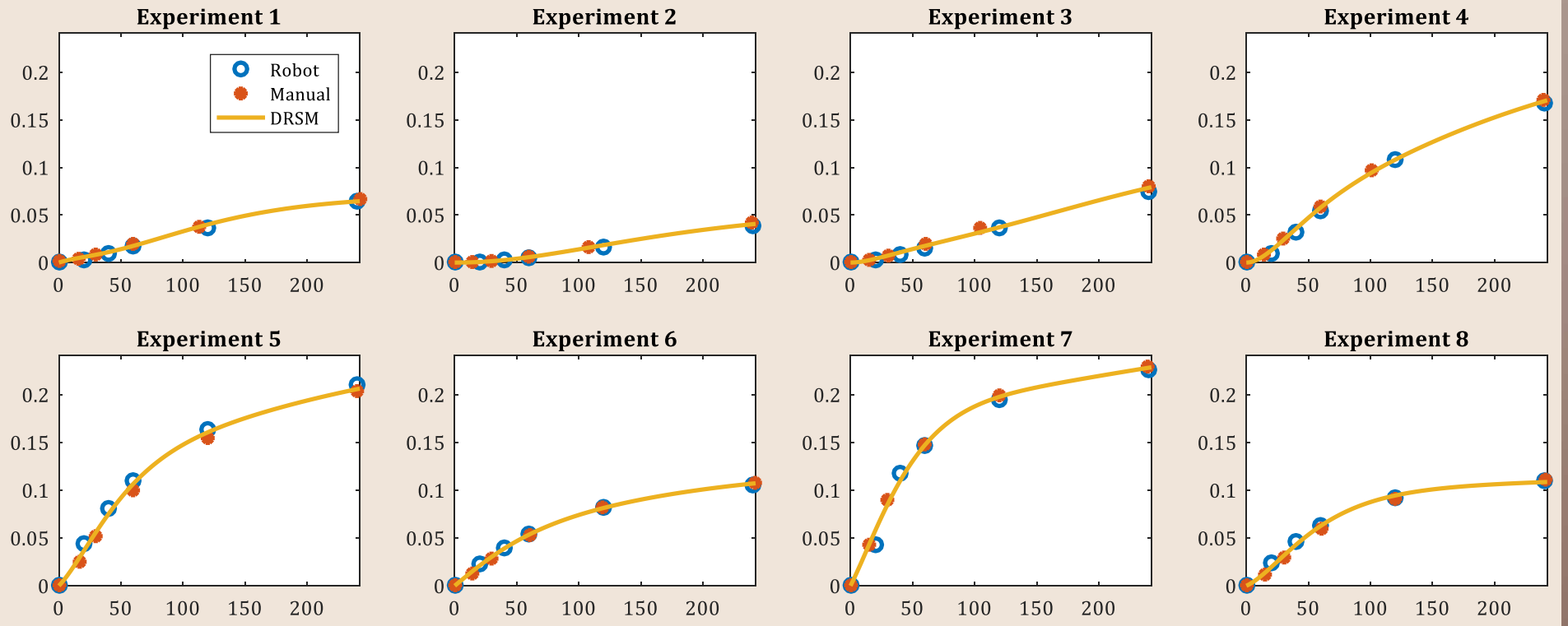
The 5 FACTORS

A: Methanol ratio, (% wt/wt solvent)
B: Starting material, wt% **C**: Base, wt%
D: Water wt% **E**: Temperature

- ¼ **Fractional factorial design**: 2^{5-2} design
  - 8 experiments
  - Aliasing Structure: D = AB, and E = AC

2FI Model: Species B

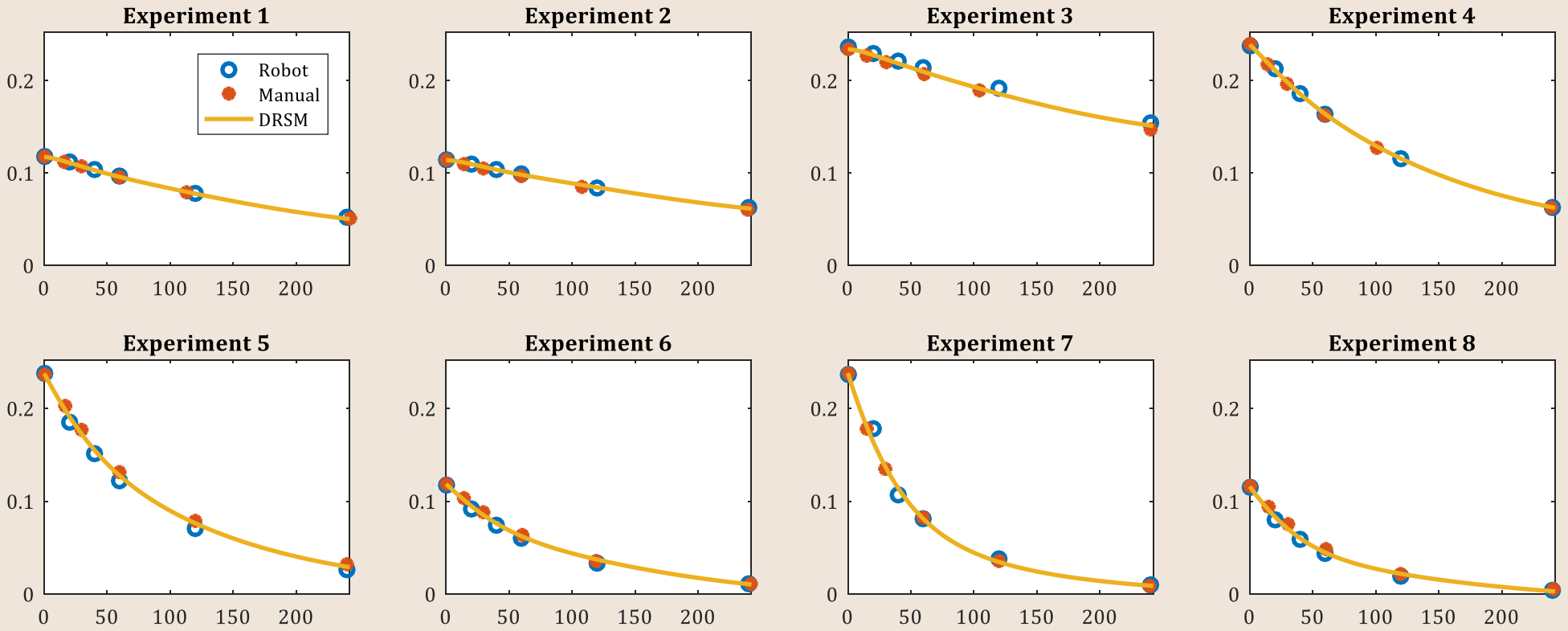
LoF *p*-value = 0.99 ➔ Perfect model



$$\tilde{y}(t) = \beta_0(t) + \beta_A(t)A + \beta_B(t)B + \beta_C(t)C + \beta_D(t)D + \beta_E(t)E +$$
$$+\boldsymbol{\beta_{BC}(t)BC + \beta_{CD}(t)CD}$$

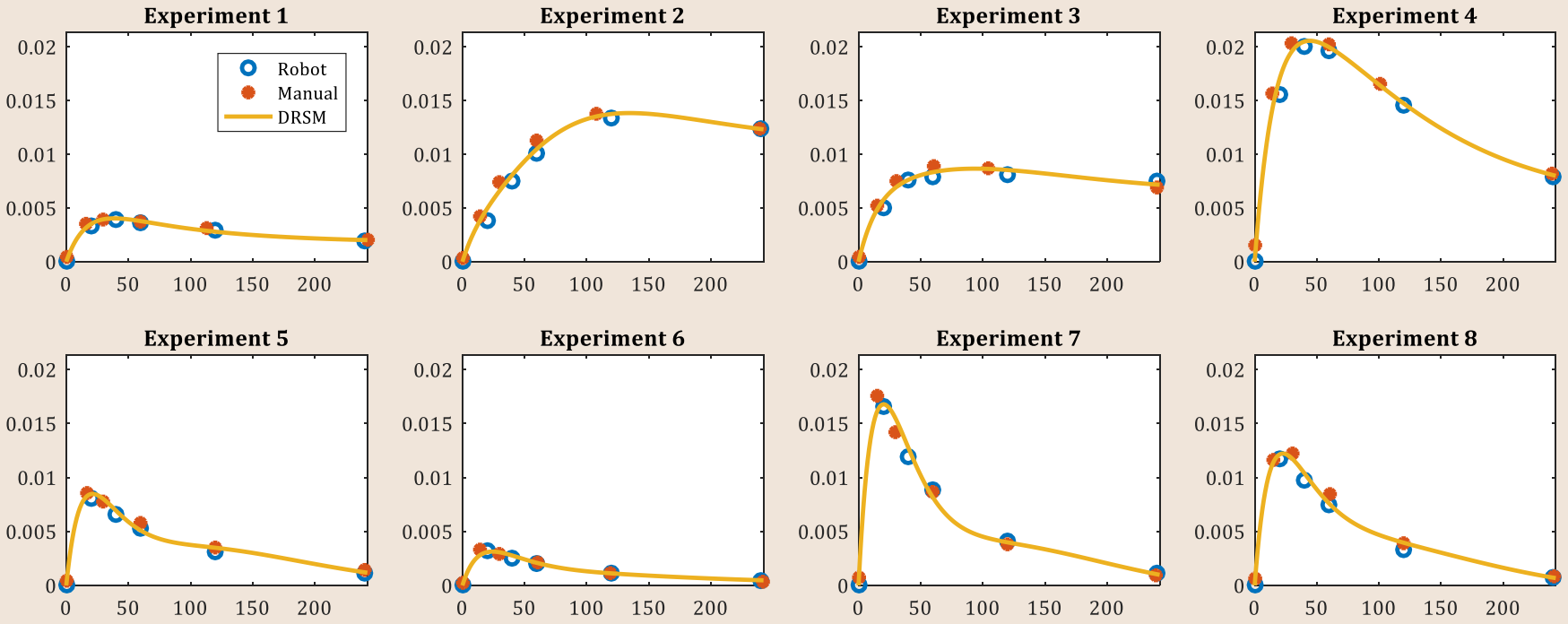
2FI Model: Species A

LoF *p*-value = 0.99 ➔ Perfect model



2FI Model: Species C

LoF *p*-value = 0.06 ➔ Good Model



$$\tilde{y}(t) = \beta_0(t) + \beta_A(t)A + \beta_B(t)B + \beta_C(t)C + \beta_D(t)D + \beta_E(t)E +$$
$$+\boldsymbol{\beta_{BC}(t)BC + \beta_{CD}(t)CD}$$

Block Effect Insignificant: Robotic vs. Manual Operation

DRSM ⟹ Reaction Knowledge

from **Data** to … **Knowledge**

From DRSM Models DISCOVER Stoichiometry and Kinetics

- Simple Semi-Batch Reactor Example → $\begin{cases} R1:\ A + B \rightarrow C \\ R2:\ 2B \rightarrow D \\ R3:\ C \rightarrow E \end{cases}$
  - Five DRSMs for $C_A(t), \ldots, C_E(t)$,

$$y_A(t) = \beta_{A0}(t) + \sum_{i=1}^{n} \beta_{Ai}(t) X_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta_{Aij}(t) X_i X_j + \sum_{i=1}^{n} \beta_{Aii}(t) X_i^2$$

$$\vdots$$

$$y_E(t) = \beta_{E0}(t) + \sum_{i=1}^{n} \beta_{Ei}(t) X_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta_{Eij}(t) X_i X_j + \sum_{i=1}^{n} \beta_{Eii}(t) X_i^2$$

- Calculate Derivatives with Time for ALL Models

$$y'_A(t) = \beta'_{A0}(t) + \sum_{i=1}^{n} \beta'_{Ai}(t) X_i + \sum_{i=1}^{n} \sum_{j=i+1}^{n} \beta'_{Aij}(t) X_i X_j + \sum_{i=1}^{n} \beta'_{Aii}(t) X_i^2$$

Rate Data ⟹ Stoichiometry

- Rates of appearance for Each Species

$$\rightarrow \begin{cases} Rxn1:\ A + B \rightarrow C \\ Rxn2:\ 2B \rightarrow D \\ Rxn3:\ C \rightarrow E \end{cases}$$

- $\boldsymbol{D}_k = \begin{pmatrix} r_{Ak}(t_1) & r_{Bk}(t_1) & r_{Ck}(t_1) & r_{Dk}(t_1) & r_{Ek}(t_1) \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ r_{Ak}(t_i) & r_{Bk}(t_i) & r_{Ck}(t_i) & r_{Dk}(t_i) & r_{Ek}(t_i) \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ r_{Ak}(t_{n_K}) & r_{Bk}(t_{n_K}) & r_{Ck}(t_{n_K}) & r_{Dk}(t_{n_K}) & r_{Ek}(t_{n_K}) \end{pmatrix}$

$$t_i = i\Delta t \quad i = 1, \dots, n_K \quad \Delta t = 1/n_K$$

  - For $n_K = 100$ matrix D_k is a 100×5
- Data Matrix for Rates of ALL Species and ALL Experiments: R_c
  - $\boldsymbol{R}_c = \begin{pmatrix} \boldsymbol{D}_1 \\ \boldsymbol{D}_2 \\ \vdots \\ \boldsymbol{D}_{n_e} \end{pmatrix}$ D_k = Data from k−th experiment $k = 1, 2, \dots, n_e$
  - For $n_e = 9$ experiments R_c is a 900×5 matrix
- SVD=Singular Value Decomposition of $\boldsymbol{R}_c$

Number of Significant SVs = ?

  - $\boldsymbol{R}_c = \boldsymbol{U\Sigma V}^{\mathrm{T}},\ \Sigma = \begin{pmatrix} \sigma_1 & 0 & 0 \\ 0 & \ddots & 0 \\ 0 & 0 & \sigma_5 \end{pmatrix}$, $\boldsymbol{U\Sigma V}^{\mathrm{T}}$ $sizes: 900X5, 5X5$ & $5X5$

SVD: $\boldsymbol{R_c = U\Sigma V^{\mathrm{T}}}$ & Projections

- # of Reactions ⇔ Significant σ_i Values= 3
  - $\boldsymbol{R_c = U_3 \Sigma_3 V_3^T}$ $\quad \boldsymbol{V_3^T} = \begin{pmatrix} \boldsymbol{v_1^T} \\ \boldsymbol{v_2^T} \\ \boldsymbol{v_3^T} \end{pmatrix} = \begin{pmatrix} 0.41 & 0.84 & -0.26 & -0.21 & -0.15 \\ -0.26 & 0.21 & 0.79 & -0.23 & 0.50 \\ 0.60 & -0.28 & 0.01 & 0.44 & -0.61 \end{pmatrix}$
- **IS (-1,-1,1,0,0) a Linear Combination of the $\boldsymbol{V_3^T}$ rows ?**
- Projection Matrix: $P = \boldsymbol{V_3^T V_3}$
- Projection of Candidate Stoichiometry: $\boldsymbol{n_{ir} = n_i V_3^T V_3}$
- Is it TRUE that: $\boldsymbol{n_{ir} \cong n_i}$?
- Projection Score: $PS = 100\{1 - \|\boldsymbol{n_{ir} - n_i}\|/\|\boldsymbol{n_i}\|\}$
  - **PS ≥ 90 is GOOD**

Initial & Sequential Projections

- **PREPARATION** of Data
  - Rate Data Matrix $\boldsymbol{R}_c$ of size $n_d \times n_s$
    - n_d = # of Data, n_s = # of species
  - Number of Significant Singular Values (sSVs)
    - Statistical Determination via an *F*-test = n_{ssvs}
      - Malinowski, *J. of Chemometrics.* 1989; **3**(1):49-60
  - Define Candidate Stoichiometries
- **INITIAL** Projection Step
  - Calculate Projection Scores (PC)
    - Accept n_i Reactions with PC≥90
  - Subtract from Rate Data Contribution of Identified Rxns
- **SEQUENTIAL** Projection Step: Repeat above

Identifying Pfizer Stoichiometries

Additive error = 0.005 on Concentrations $0.005 < C_i(t_k) < 0.9$

Scores of **True** reactions		
1	A + B⇆ C + D	96.5
2	C → D + E	90.8
3	E → F	92.3
4	B + D ⇆ G	99.1
5	G → D + H	96.3
6	A + F → I	**82.4**
7	2A → J	**77.4**
8	B + J → 2E + I	**24.8**

Scores of **Untrue** reactions		
1	A → J	**57.6**
2	C → J	**38.8**
3	2A + B → J	**72.5**
4	J → 2D + I	**65.0**
5	B + J → E + I	**21.2**
6	B + J → D + I	**51.2**

Blind Test: Excellent Result

$\text{Score}_i = 100(1 - \|\boldsymbol{n}_{ir} - n_i\|/\|\boldsymbol{n}_i\|)$

n_i= Candidate Stoichiometry

$\boldsymbol{n}_{ir}$= Response Vector

Seven (7) Significant SVs via an *F*-test

σ_i = **81, 9.7, 6.3, 1.5, 1.0, 0.92, 0.22**, 0.18, 0.15, 0.09

Identifying Pfizer Stoichiometries

NO Measurement error

Scores of True reactions (Without Measurements Error)		
1	A + B ⇆ C + D	99.5
2	C → D + E	99.0
3	E → F	99.5
4	B + D ⇆ G	99.9
5	G → D + H	99.5
6	A + F → I	99.9
7	2A → J	97.9
8	B + J → 2E + I	92.7

Scores of Untrue reactions (Without Measurement error)		
1	A → J	74.6
2	C → J	57.3
3	2A + B → J	81.9
4	J → 2D + I	82.0
5	B + J → E + I	85.8
6	B + J → D + I	88.6

Confirmation of Method

Eight (8) Significant SVs

$\sigma_i =$ **81, 9.7, 6.3, 1.5, 1.0, 0.91, 0.19, 0.10**, 0.04, 0.02

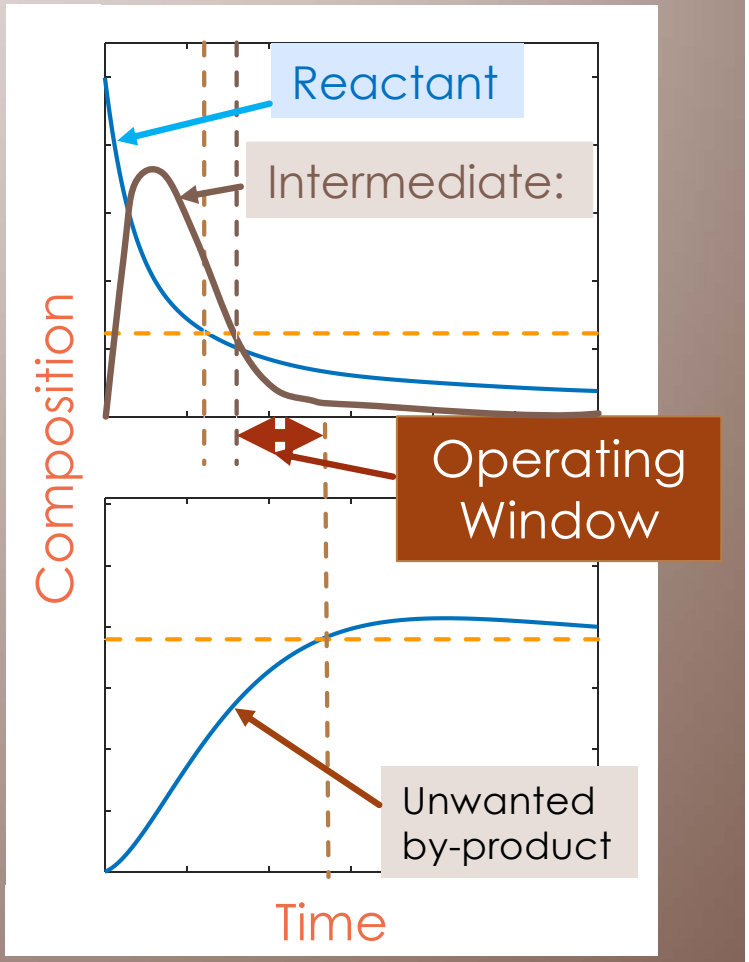
Dw

DRSM and TFA

- DRSM Makes TFA More Accurate
  - Larger Number of Significant Singular Values
    - Identifies More Reactions
- With Stoichiometries Identified
  - Calculate Rates of Each Reaction
  - Reaction Rates & $C_i(t)$ → Kinetics
    - One Reaction at a Time → MORE Accurate Model
- DRSM Enables Other Tasks
  - e.g. Optimal Operating Conditions

Process Optimization via DRSM

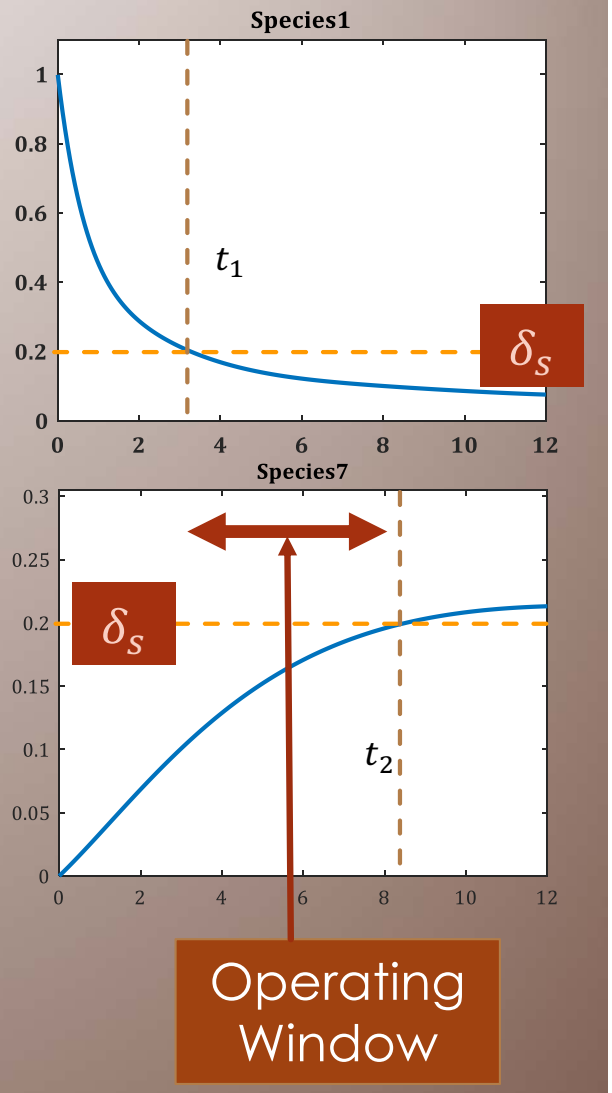
- Calculate Operating Window (OW):
  - Concentrations of Impurities Below Specs
    - Reactants
    - Intermediates
    - Unwanted by-products
- Maximize OW by Selecting
  - Operating Conditions
- Account for Uncertainties
- Peak or Area HPLC Data



Maximize Operating Window

- Optimization Results
  - When $\delta_s = 0.1$ for all species,
    - window does not exist.
  - Study different specifications

δ_s	Factor1	Factor2	Factor3	Optimal window (hr)
0.14	Infeasible			---
0.15	90	1.02	0	3.07
0.16	90	1.03	0.06	4.35
0.17	90	1.03	0.17	4.59
0.18	90	1.03	0.28	4.81
0.19	90	1.03	0.39	5.01
0.2	90	1.03	0.50	5.20



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What to Remember Tomorrow

- The Novelty of DoDE and DRSM
  - TWO Generalizations of DoE and RSM
    - DoDE: Experiments with Time Varying Inputs
    - DRSM: Modeling Time-Varying Outputs
- Stoichiometric Identification Enhanced
  - Some Current Issues
    - Implications of Unmeasured Species
    - Not Enough Candidate Stoichiometries

Thank You Very Much

May I answer your Questions